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AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 16 APRIL 2008

SUBJECT: DIFENOCONAZOLE – Occupational Exposure/Risk Assessment for a Georgia Section 18 Request to Use Difenoconazole on Cantaloupes, Watermelons and Cucumbers

PC Code: 128847

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INTRODUCTION

Under provisions in Section 18 of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended, the State of Georgia has requested an emergency exemption for use of the fungicide difenoconazole on cantaloupes, watermelons and cucumbers.

This memorandum serves as the ARIA/RD's assessment of exposure and risk to occupational pesticide handlers (mixers, loaders, applicators) and to agricultural workers. It should be noted that the risk assessment techniques used in this document are those that have been developed and refined by the HED/Office of Pesticide Programs' Science Policy Council for Exposure (ExpoSAC). Therefore, the risk assessment methods are the same as those used by HED and are HED standard operating procedure (SOP).

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USE PATTERN SUMMARY

The use pattern summary is taken from the Georgia Section 18 request (correspondence D. Langston, Univ. Ga. Coop. Ext. Serv. to D. Jones, Ga. Dept. Agricult. 24 MAR 2008) and from supplemental pesticide labeling.

The product requested for use is Inspire[®] Super MP fungicide (EPA Reg. No. 100 – 1262). Inspire[®] contains 2.08 lb active ingredient (ai) per gallon. The rate of application is 7.0 fl oz formulation/A ($2.08 \text{ lb ai/gal} \div 128 \text{ fl oz/gal} = 0.01625 \text{ lb ai/fl oz}$; $0.01625 \text{ lb ai/fl oz} * 7.0 \text{ fl oz formulation/A} = 0.11375 \text{ lb ai/A}$)

The request indicates a total of 68,000 acres may require treatment. The request also states there is a maximum of 4 applications. Therefore,
 $68,000 \text{ A} * 0.11375 \text{ lb ai/A} = 7,735 \text{ lb ai} * 4 \text{ (applications)} = 30,940 \text{ total lb ai}$ may be needed.

The section 18 request indicates applications will be foliar and applied aurally or by ground spray machinery with the preponderance being ground applications. The “parent” label lists chemigation as method of application. The Section 18 request did not list chemigation and therefore it is not assessed.

According to the label, ground applications should be made in a minimum of 10 gallons of water per acre (gpa). Aerial applications should be made in a minimum of 5 gpa.

The label directs mixers, loaders and applicators to wear personal protective equipment (PPE) consisting of a long-sleeved shirt, long pants, shoes plus socks and chemical resistant gloves.

The label lists a 7 – 10 day application interval; a 1 day preharvest interval (PHI) and a restricted entry interval (REI) of 12 hours. No more than 2 consecutive applications should be made without alternating with another fungicide with a different mode of action. Inspire[®] should be tank mixed with Vanguard WG. An assessment for the use of Vanguard will be presented in a separate document. See Table 1.0 for a summary of the proposed use pattern for difenoconazole.

| Table 1.0 Summary of Proposed Use Pattern for Difenconazole Applied to Cantaloupe, Watermelon and Cucumber | |
|-------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Formulation | Inspire [®] Super MP fungicide; Reg. No. 100 – 1262; 2.08 lb ai/gallon liquid |
| Pest | <i>Didymella bryonia</i> the fungus which causes gummy stem blight |
| Method of Applic. | Ground boom; aerial |
| Max. Applic. Rate | 7.0 fl oz formulation/A (0.11375 lb ai/A) |
| Max. No. Applications | 4 |
| Applic. Interval | 7 – 10 days |
| Preharvest Interval | 1 day |
| Restricted Entry Interval | 12 hours |
| Manufacturer | Syngenta Crop Protection |

OCCUPATIONAL PESTICIDE HANDLER EXPOSURE

Based upon the Georgia Section 18 request, ARIA/RD expects applications will be made by ground-boom sprayer and via aerial applications. According to the request, most applications are expected to be ground applications. As such, the most highly exposed occupational pesticide handlers are believed to be: 1) mixer/loaders using open-pour loading of liquids, 2) applicators using open-cab tractors with ground-boom sprayers, and 3) aerial applicators.

Since most of the applications are expected to be made by ground machinery, most are expected to be made by private (i.e., grower) occupational handlers. Aerial applications are assumed to be made by commercial applicators. Since the total number of acre treatments is comparatively small, no more than two consecutive applications may be made, and the treatment window is from March to October, ARIA/RD expects short-term duration exposures (1-30 days) for occupational pesticide handlers.

No chemical specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the Pesticide Handlers Exposure Database (PHED, v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for “baseline” that is, for workers wearing a single layer of work clothing consisting of a long sleeved shirt, long pants, shoes plus socks and no protective gloves as well as for “baseline” **and the use of protective gloves** or other PPE as might be necessary. Label required PPE was discussed earlier.

Particularly for ground applications, private (i.e., grower) applicators may perform all functions, that is, mix, load and apply the material. HED ExpoSAC standard procedure directs that although the same individual may perform all those tasks, they shall be assessed separately. The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the PHED Surrogate Exposure Guide (August

1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be conducted by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of PPE for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (*e.g.*, chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

The toxicological parameters used herein are taken from: M. Sahafeyan *et al.*, 9 NOV 2007, DP 346591, "Difenoconazole in/on Fruiting Vegetables, Pome Fruit, Sugar Beets, Tuberous and Corm Vegetables, and Imported Papaya. Health Effects Division (HED) Revised Risk Assessment."

The dermal toxicological endpoint was identified for a rat dietary study where the effects were reduced body weights in the F₀ females prior to mating, gestation and lactation. The No Observable Adverse Effect Level (NOAEL) is 1.25 mg ai/kg bw/day for short-term and intermediate-term exposures. A dermal absorption factor of 15.3 % was identified using the *in vivo* method through rat skin.

The short- and intermediate-term inhalation toxicological endpoints are identified from the same rat reproductive toxicity study. The toxic effects are the same and the NOAEL is also 1.25 mg ai/kg bw/day. HED and RD assume 100 % absorption via the inhalation route of exposure.

Since the dermal and inhalation toxicological effects are the same and are identified from the same study, the dermal and inhalation exposures are summed before being used to calculate the Margin of Exposure (MOE).

Difenoconazole is classified as a Group "C", possible human carcinogen and HED recommends a non-linear (MOE) approach for human risk assessment (CPRC Document, 7/27/94, Memo P.V. Shah, 3 MAR 2007, HED Doc. No. 0054532). Therefore, since long-term (*i.e.*, chronic exposure) is not expected, a cancer risk assessment is not necessary. See Table 2.0 for a summary of exposures and risk to occupational pesticide handlers. See the ATTACHMENT for a summary of toxicological endpoints used for risk assessment.

A MOE of 100 is adequate to protect occupational pesticide handlers from short-term exposures to difenoconazole.

| Table 2.0 Estimated Handler Exposure and Risk from the Proposed Uses of Difenconazole | | | | | |
|---------------------------------------------------------------------------------------|------------------------------|------------------------------------------|---------------------------------------------------------|--------------------------------------------|-----------------------------------------|
| Unit Exposure ¹ mg a.i./lb handled | Applic. Rate ² | Units Treated ³ Per Day | Average Daily Dose ⁴ mg a.i./kg bw/day | NOAEL ⁵ mg a.i./kg bw/day | MOE ⁶ SHORT-TERM |
| <i>Mixer/Loader - Liquid - Open-pour</i> | | | | | |
| Dermal: SLNoGlove 2.9 SLWGloves 0.023 Inhal 0.0012 | 0.11375 lb ai/A | 350 A/day | SLNoGlove 0.25 SLWGlove 0.002 Inhal 0.00068 | 1.25 | SLNoGlove 5 SLWGlove 466 |
| <i>Applicator - Ground-boom - Open Cab</i> | | | | | |
| Dermal: SLNoGlove 0.014 SLWGloves 0.014 Inhal 0.00074 | 0.11375 lb ai/A | 200 A/day | SLNoGlove 0.00069 SLWGlove 0.00069 Inhal 0.00024 | 1.25 | SLNoGlove 1,344 SLWGlove 1,344 |
| <i>Applicator - Fixed-wing - Aerial (Pilots not required to wear gloves)</i> | | | | | |
| Dermal: SLNoGlove 0.0050 Inhal 0.000068 | 0.11375 lb ai/A | 350 A/day | SLNoGlove 0.00044 Inhal 0.000039 | 1.25 | SLNoGlove 2,610 |

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. Dermal: SLNoGlove = Single layer work clothing (long pants, long-sleeved shirt, shoes plus socks) No gloves; SLWGloves = single layer work clothing WITH the use of protective gloves; Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled.

2. Applic. Rate. = Taken from Georgia Section 18 Request

3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; SOP No. 9.1. ExpoSAC; Revised 5 July 2000;

4. Average Daily Dose = Unit Exposure * Applic. Rate * Units Treated * absorption factor (15.3 % dermal absorption) ÷ Body Weight (70 kg).

5. NOAEL = No Observable Adverse Effect Level 1.25 mg a.i./kg bw/day for short-term dermal and short-term inhalation

6. MOE = Margin of Exposure = NOAEL ÷ ADD. ADD = dermal + inhalation

A MOE of 100 is adequate to protect occupational pesticide handlers from exposures to difenoconazole. Provided handlers wear protective gloves as specified on the label, all MOEs are > 100. Therefore the proposed uses do not exceed ARIA/RD's level of concern.

POST-APPLICATION EXPOSURE TO AGRICULTURAL WORKERS

It is possible for agricultural workers to have post-application exposures to pesticide residues during the course of typical agricultural activities. HED in conjunction with the Agricultural Re-entry Task Force (ARTF) has identified a number of post-application agricultural activities that may occur and which may result in post-application exposures to pesticide residues. HED has also identified Transfer Coefficients (TC) (cm²/hr) relative to the various activities which express the amount of foliar contact over time,

during each of the activities identified. For the proposed crop use sites, the highest TC identified is 2,500 cm²/hr for hand harvesting.

The TCs used in this assessment are from an interim TC Standard Operating Procedure (SOP) developed by HED's ExpoSAC using proprietary data from the ARTF database (SOP # 3.1). It is the intention of HED's ExpoSAC that this SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

Lacking compound specific dislodgeable foliar residue (DFR) data, HED assumes 20 % of the application rate is available as DFR on day zero after application. This is adapted from the ExpoSAC SOP No. 003 (7 May 1998 - Revised 7 August 2000).

The following convention may be used to estimate post-application exposure.

$$\text{Average Daily Dose (ADD) (mg a.i./kg bw/day)} = \text{DFR } \mu\text{g/cm}^2 * \text{TC cm}^2/\text{hr} * \text{hr/day} * 0.001 \text{ mg}/\mu\text{g} * 1/70 \text{ kg bw}$$

and where:

$$\text{Surrogate Dislodgeable Foliar Residue (DFR)} = \text{application rate} * 20\% \text{ available as dislodgeable residue} * (1-D)^t * 4.54 \times 10^8 \mu\text{g/lb} * 2.47 \times 10^{-8} \text{ A/cm}^2.$$

$$0.11375 \text{ lb a.i./A} * 0.20 * (1-0)^0 * 4.54 \times 10^8 \mu\text{g/lb} * 2.47 \times 10^{-8} \text{ A/cm}^2 = 0.26 \mu\text{g/cm}^2, \text{ therefore,}$$

$$0.26 \mu\text{g/cm}^2 * 2,500 \text{ cm}^2/\text{hr} * 8 \text{ hr/day} * 0.001 \text{ mg}/\mu\text{g} * 0.153 \text{ (15.3 \% dermal absorption)} \div 70 \text{ kg bw} = 0.011 \text{ mg/kg bw/day}.$$

$$\text{MOE} = \text{NOAEL} \div \text{ADD} \text{ then } 1.25 \text{ mg/kg bw/day} \div 0.011 \text{ mg/kg bw/day} = 114.$$

A MOE of 100 is adequate to protect agricultural workers from post-application exposures. The MOE is > 100 therefore the proposed use does not exceed ARIA/RDs level of concern.

RESTRICTED ENTRY INTERVAL (REI)

Difenoconazole is classified in acute Toxicity Category III for acute dermal toxicity and primary eye irritation. It is classified in Toxicity Category IV for acute inhalation toxicity and primary skin irritation. It is negative as a dermal sensitizer. Therefore, the interim worker protection standard (WPS) REI of 12 hours is adequate to protect agricultural workers from a most of post-application exposures to difenoconazole. The draft Inspire[®] label lists the REI as 12 hours.

ATTACHMENT

| Table 3.4.12b Summary of Toxicological Doses and Endpoints for Difenconazole for Use in Occupational Human Health Risk Assessments | | | | |
|-------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Exposure Scenario | Point of Departure | Uncertainty/FQPA Safety Factors | RfD, PAD, Level of Concern for Risk Assessment | Study and Toxicological Effects |
| Dermal Short- and Intermediate-Term (1-30 days and 1-6 months) | Oral NOAEL = 1.25 mg/kg/day Dermal Absorption factor=15.3% | $UF_A = 10X$ $UF_H = 10X$ $UF_{FQPA} = 1X$ | Occupational LOC for MOE<100 | Reproduction and fertility effects (rat; dietary) Offspring LOAEL = 12.5 mg/kg/day based on reduction in body weight gain of F ₀ females prior to mating, gestation and lactation |
| Dermal Long-Term (>6 months) | Oral NOAEL = 0.96 mg/kg/day Dermal Absorption factor=15.3% | $UF_A = 10X$ $UF_H = 10X$ $UF_{FQPA} = 1X$ | Occupational LOC for MOE<100 | Combined chronic toxicity/carcinogenicity (rat; dietary) LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body weight gains |
| Inhalation (Short- and Intermediate-term) | Oral NOAEL = 1.25 mg/kg/day 100% inhalation absorption assumed | $UF_A = 10X$ $UF_H = 10X$ $UF_{FQPA} = 1X$ | Occupational LOC for MOE<100 | Reproduction and fertility effects (rat; dietary) Offspring LOAEL = 12.5 mg/kg/day based on reduction in body weight gain of F ₀ females prior to mating, gestation and lactation |
| Inhalation (Long- term) | Oral NOAEL = 0.96 mg/kg/day 100% inhalation absorption assumed | $UF_A = 10X$ $UF_H = 10X$ $UF_{FQPA} = 1X$ | Occupational LOC for MOE<100 | Combined chronic toxicity/carcinogenicity (rat; dietary) LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body weight gains |
| Cancer (oral, dermal, inhalation) | Difenconazole is classified as a Group C, possible human carcinogen with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3, 2007, HED Doc. No. 0054532) | | | |

Abbreviations: UF = uncertainty factor, UF_A = extrapolation from animal to human (interspecies), UF_H = potential variation in sensitivity among members of the human population (intraspecies), UF_{FQPA} = FQPA Safety Factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, RfD = reference dose (a = acute, c = chronic), PAD = population adjusted dose, MOE = margin of exposure, LOC = level of concern

NOTE: The toxicological parameters used herein are taken from: M. Sahafeyan et al., 9 NOV 2007, DP 346591, "Difenconazole in/on Fruiting Vegetables, Pome Fruit, Sugar Beets, Tuberous and Corm Vegetables, and Imported Papaya. Health Effects Division (HED) Revised Risk Assessment."

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